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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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08/477,983 06/07/95 RUBIN

J 40399/321/NI

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HM12/0313

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EXAMINER

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SADUD, C

ART UNIT

PAPER NUMBER

1647

34

DATE MAILED:

03/13/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.
08/477,983

Applicant(s)
RUBIN et al.

Examiner
Christine J. Saoud

Group Art Unit
1647



☒ Responsive to communication(s) filed on Dec 22, 2000

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 92-108 is/are pending in the application.

Of the above, claim(s) 107 and 108 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 92-106 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been
☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

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DETAILED ACTION

Transitional After Final Practice

1. Since this application is eligible for the transitional procedure of 37 CFR 1.129(a), and the fee set forth in 37 CFR 1.17(r) has been timely paid, the finality of the previous Office action is hereby withdrawn pursuant to 37 CFR 1.129(a). Applicant's second submission after final filed on 22 December 2000 has been entered.

Response to Amendment

2. Claims 44-79 and 81-91 have been canceled and claims 92-108 have been added as requested in the amendment of paper #32, filed 22 December 2000. Claims 92-108 are pending in the instant application.

Election/Restriction

3. Newly submitted claims 107-108 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: claims 107-108 are directed to methods of recombinant production of KGF comprising expressing a DNA. The invention which is under examination is the isolated protein which is related to the newly submitted invention as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product as claimed can be made by another and

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materially different process (MPEP § 806.05(f)). In the instant case the claimed product could be isolated from nature, rather than recombinantly produced as claimed. Search burden is supported by the fact that the inventions are differently classified (530/350 for the protein and 435/69.4 for the method of production).

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 107-108 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

6. Applicant's arguments filed 24 May 2000 (as they relate to the new claims) have been fully considered but they are not deemed to be persuasive.

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Double Patenting

7. Claims 92-106 of this application conflict with claims 76, 77, 79, 84, 88-118, and 123-146 of Application No. 08/455,620. 37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822.

8. Claims 92-106 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 76, 77, 79, 84, 88-118, and 123-146 of copending application Serial No. 08/455,620 because the claims of both applications are directed to the same protein, KGF comprising the amino acid sequence of Figure 7 (including modified and variant forms).

It is noted that the claims in both of the above applications (08/477,983 and the instant application 08/455,620) are both directed to the same invention, keratinocyte growth factor. The claims are in a state of flux, therefore, it is not clear if there are any same invention double patenting rejections to be made at this time. Applicant is advised that if identical claims are submitted in the two applications, they will be rejected for provisional double patenting, which cannot be overcome by the filing of a terminal disclaimer. A rejection of this nature would not be considered a new grounds of rejection because it would be necessitated by Applicant's amendments to the claims.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

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Applicant acknowledges the provisional obviousness-type double patenting rejection and indicate that the issue will be attended to upon indication of subject matter that would be allowed. Applicant should note that claims 96 and 103-105 are only rejected for the provisional obvious-type double patenting issue. Further, Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822. No such "clear line of demarcation" is present in the instant situation. Any response which does not provide for such may be interpreted as a non-responsive to this requirement.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 92-93 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant specification fails to convey the subject matter of the instant claims 92-93. Applicant is invited to point to the page and line numbers of the specification which support the invention as presently claimed. For example, a written description of a polypeptide segment

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which is useful in producing antibodies wherein the portion is not part of aFGF, bFGF, EGF, TGF-alpha, GCF, MCF or IL3 could not be found in the specification as originally filed. No disclosure of peptide segments useful for producing an antibody that selectively binds to KGF could not be found in the specification as originally filed.

10. Claims 94-95 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for KGF of Figure 7 (with or without the signal peptide of amino acids 1-31) and KGF polypeptides which are truncated within the region of amino acids 32-78, does not reasonably provide enablement for a polypeptide which comprises amino acids 32-78 of Figure 7, has a molecular weight of 16-30 kDa and has mitogenic activity on keratinocyte cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification teaches a keratinocyte growth factor (KGF) of 194 amino acids in length and DNA encoding said KGF. The specification also teaches that the first 31 amino acids are a signal sequence that is cleaved in the mature protein and that amino acids 32-78 confer epithelial cell specificity to the protein.

Claims 94-95 are directed to KGF polypeptides which have a molecule weight of 16-30 kDa, comprises amino acids 32-78 of Figure 7, and has a specific biological activity. However, the instant specification only provides for a single KGF molecule that has a very specific stimulatory activity on these cells which has an amino acid sequence as disclosed in Figure 7.

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However, the instant claims encompass variants of the disclosed protein wherein the only defined structure is the presence of amino acids 32-78, which does not confer the biological activity required by the claims. It would require undue experimentation for one of ordinary skill in the art to determine which proteins which meet the structural limitations of the claims would also meet the functional limitations. The instant specification lacks the appropriate guidance to alter the disclosed protein and obtain one with the required activity. The instant specification defines KGF as including mutants and or having and at least one or more amino acid differences. (see pages 7 and 10). However, the specification is only enabling for KGF having the amino acid sequence found in Figure 7 (or specific portions as outlined above) because it does not describe the production of any KGF *lacking* that sequence.

In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970), held that

“Inventor should be allowed to dominate future patentable inventions of others where those inventions were based in some way on his teachings, since such improvements while unobvious from his teachings, are still within his contribution, since improvement was made possible by his work; however, he must not be permitted to achieve this dominance by claims which are insufficiently supported and, hence, not in compliance with first paragraph of 35 U.S.C. 112; that paragraph requires that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific law; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.”

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By following the guidance presented in the instant specification and sound scientific principles, a practitioner can not produce a KGF lacking the disclosed amino acid sequence and predict the functional properties of that protein.

Additionally, the pending claims encompass non-naturally occurring mutants of KGF having the disclosed amino acid sequence but does not explicitly identify those amino acid residues which are critical for the biological activity of KGF (except for amino acids 32-78 which confer specificity). In the absence of guidance, a practitioner of the art of molecular biology would have to resort to a substantial amount of experimental trial and error in the form of deletional and substitutional analysis to identify those critical residues as would be needed to produce a mutant of the disclosed KGF protein (except for N-terminal truncations of amino acids 32-78). This trial and error would clearly constitute undue experimentation and, therefore, the instant specification is not enabling for the production of such mutants, which are clearly intended by the use of the KGF polypeptide in the claims. The standard for an enabling disclosure is not one of making and testing and the claims constitute a "wish to know". In so far as the instant claims encompass a KGF protein having a sequence other than the disclosed sequence identified above, specific case law bears on this issue: Amgen Inc. v. Chugai Pharmaceuticals Co. Ltd., 18 U.S.P.Q. 2d, 1016, held that;

"A gene is a chemical compound, albeit a complex one, and it is well established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials, and describe how to obtain it. *See Oka*, 849 F.2d at 583, 7 USPQ2d at 1171. Conception does not occur unless one has a mental picture of the structure of the chemical, or is able to define

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it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by its principal biological property, *e.g.*, encoding human erythropoietin, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. We hold that when an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, *i.e.*, until after the gene has been isolated.”

The fact pattern is directly analogous in that what is claimed are proteins that have yet to be isolated or characterized for the activity recited in the application and thereby constitutes a “wish to know” rather than a reduction to practice, absent evidence to the contrary. *In re Clarke*, 148 USPQ 665, (CCPA 1966) held that;

It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. *In re Soll*, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189 ; *In re Wahlforss et al.*, 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397 . The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of a small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably large number of reductions to practice would probably be necessary.

11. Claims 92 and 93 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

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With regard to claim 92, the instant specification is not enabled for “antibodies that selectively bind said polypeptide”, because selectively binding to the exclusion of all other polypeptides would require a knowledge of the amino acid sequence of all proteins that exist, and this information is not present in the instant specification or in the art of record. This rejection is being made due to the ambiguity of the recitation of “selectively bind”; see 112/2nd rejection below. In addition, it is not clear that the specification enables segments of the amino acid sequence of Figure 7 that would produce an antibody that would not significantly cross react with other proteins because there is so much similarity between the protein of Figure 7 and other FGF family members. Lastly with regard to claim 93, a sequence comparison of the amino acid sequence with the sequences of other proteins in a database reveals at least 50 different proteins that share stretches of at least 5 amino acids, which is sufficient to produce an antibody. Furthermore, the specification fails to teach segments which are useful in producing antibodies and wherein the segment is not a portion of the other growth factors mentioned in the claim. Therefore, without a specific recitation of a length for the “segment”, it would appear that a generic segment would not be enabled for producing an antibody that was selective, absent evidence to the contrary.

Claim 93 does not recite any structure for the polypeptide being claimed except that the protein (from which the portion is derived) has a molecular weight of 16-30 kDa and is called KGF. The instant specification is not enabled for any KGF polypeptide except for the polypeptide of Figure 7 (see arguments above with regard to the scope rejection of claims 94-95).

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12. Claims 97-102 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a substitution at an amino acid within amino acids 65-157 or amino acids 161-189 of Figure 7 wherein the polypeptide has mitogenic activity on BALB/MK keratinocyte cells, does not reasonably provide enablement for those polypeptides which comprise a conservative substitution which do not retain biological activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant claims encompass mutant polypeptides which comprise “a conservative substitution”. However, it is not clear what type of substitution would be considered “conservative” because a number of activities or structures could be conserved. Therefore, this language is indefinite (see 112/2nd rejection below). In addition, the instant specification only teaches how to use those polypeptides having a “conservative” substitution in which biological activity is conserved. As stated, “conservative” could refer to conservation of amino acid structure, antigenic activity, receptor binding activity, cell proliferation activity, etc. Because the specification only teaches how to use KGF polypeptides which are mitogenic for BALB/MK keratinocyte cells, it would require undue experimentation to use the claimed invention if this activity is not retained.

13. Claims 92, 97-102, 106 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which

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applicant regards as the invention. Any claim which is not specifically recited below is indefinite for depending on an indefinite claim because the further limitations of the dependent claims do not correct the deficits indicated below.

Claim 92 is indefinite for the recitation of “selectively bind”. The metes and bounds of this claim cannot be determined because it is not clear what is meant by “selectively”. If this recitation means that the antibody binds to the polypeptide to the exclusion of all other proteins, then the claims are not enabled (see above). If this recitation means that the antibody binds to the polypeptide such that the antibody does not significantly react with other KGF polypeptides or does not significantly react with other polypeptides in general, the claims do not reflect this distinction.

Claim 97 is indefinite for the recitation of “conservative substitution”. The metes and bounds of this claim cannot be determined because it is not clear what is being conserved. For example, amino acid structure could be conserved without conservation of biological activity; antigenicity could be conserved without conservation of amino acid structure; receptor binding activity could be conserved without conservation of mitogenic activity, etc. Therefore, in the absence of what function is being conserved, the claim is indefinite (as well as the claims which depend therefrom).

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Conclusion

14. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Saoud, Ph.D., whose telephone number is (703) 305-7519. The examiner can normally be reached on Monday to Friday from 7AM to 3PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers.

Official papers filed by fax should be directed to (703) 308-4556. If this number is out of service, please call the Group receptionist for an alternate number. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. Official papers should NOT be faxed to 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

March 12, 2001

**CHRISTINE J. SAOUD
PRIMARY EXAMINER**

Christine J. Saoud